DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-901/S-002

Galderma Laboratories, L.P.
Attention: Christine Shank
Senior Director, Regulatory Submissions
14501 North Freeway
Fort Worth, Texas 76177

Dear Ms. Shank:

Please refer to your supplemental new drug application dated November 10, 2003, received November 12, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MetroLotion® (metronidazole lotion) Topical Lotion, 0.75%.

This "Changes Being Effected" supplemental new drug application provides for changes to the Pharmacokinetics subsection to furnish adequate information for the safe and effective use of the drug as requested in the Agency letter dated March 26, 2003.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 10, 2003.

Revisions to the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the labeling as requested in our letter dated April 27, 2000, has not been implemented with the current labeling submission.

Please revise the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the labeling as follows:

> "Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats. Metronidazole has not been assessed for carcinogenic activity following topical administration. In several long term studies in mice, oral doses of approximately 200 mg/m²/day (approximately 20 times the exposure of a patient that received the estimated maximum human topical daily dose (assuming 100% bioavailability and following normalization of the data on the basis of the body surface area)) or greater were associated with increase incidences of lung tumors in male mice and lymphomas in female mice. In several long-term studies in rats, oral administration of metronidazole resulted in increased incidences of mammary and hepatic tumors in female rats and testicular tumors and pituitary adenomas in male rats at dosages of approximately 1600 mg/m²/day (approximately 170 times the exposure of a patient that received the estimated maximum human topical daily dose (assuming 100% bioavailability and following normalization of the data on the basis of the body surface area)) or greater. In another oral study, an increased of mammary tumors was observed in female rats that received approximately 160 mg/m² day (approximately 17 times the exposure of a patient that received the estimated maximum human topical daily dose

(assuming 100% bioavailability and the following normalization of the data on the basis of the body surface area)).

Ultraviolet radiation-induced carcinogenesis was enhanced in albino mice by intrperitoneal injection of metronidazole ata a dosage of 45 mg/m²/day, 5 days per week for 10 weeks, as indicated by a decreased latency period to the development of skin neoplasms. It is unclear how this level of exposure compares to the clinical situation with respect to the concentration of the drug or metabolics i the skin. This study did not determine if metronidazole must be present during exposure to ultraviolet radiation in order to enhance tumor formation; metronidazole may promote tumor formation in cells that have previously been initiated by ultraviolet radiation.

Matronidazole exhibited mutagenic activity in several in vitro bacterial and mammalian assay systems. Intraperitoneal administration of metronidazole to mice resulted in a dosage-dependent increase in the incidence of chromosomal aberrations in peripheral lymphocytes was reported in patients with Crohn's disease who were treated with metronidazole for 1 to 24 months at a dosage of 200 to 1200 mg/day. However, similar results were not observed in another study, in which humans were treated for 8 months.

In rats, oral metronidazole at a dosage of approximately 1800 mg/m²/day (approximately 200 times the exposure of a patient that received the estimated maximum human topical daily dose (assuming 100% bioavailability and following normalization of the data on the basis of body surface area)) induced inhibition of spermatogenesis and severe testicular degeneration."

These changes should be made at the next printing.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
5/11/04 02:35:25 PM
Signing off for Dr. Wilkin, Division Director